2-MERCAPTOBENZOTHIAZOLE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 149-30-4

Chem. Abstr. Serv. Name:

2-Mercaptobenzothiazole

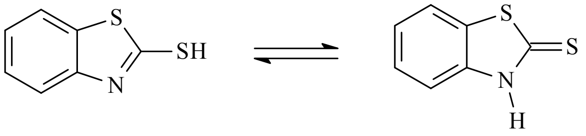
IUPAC Systematic Name:

3*H*-1,3-Benzothiazole-2-thione

Synonyms: Benzothiazole-2-thiol; 1,3-benzothiazole-2-thiol; 2-benzothiazolethiol; 3*H*-benzothiazole-2-thione; 2-sulfanylbenzothiazole

Acronyms: MBT; 2-MBT.

1.1.2 Structure and molecular formula, and relative molecular mass



(tautomers in crystals and aqueous solutions)

Molecular formula: $C_7H_5NS_2$

Relative molecular mass: 167.25

1.1.3 Physical and chemical properties of the pure substance

Description: Yellowish crystals or powder with a characteristic sulfurous odour (IFA, 2015)

Melting point: 180–182 °C (HSDB, 2015)

Density (at 20 °C): 1.42 g/cm^3 (HSDB, 2015)

Octanol/water partition coefficient: log K_{ow}, 2.41 (HSDB, 2015)

Water solubility: Moderately soluble (100–1000 mg/L) (ECHA, 2015)

Dissociation constant: pK_a 7.0 at 20 °C (HSDB, 2015)

Volatility: Vapour pressure, 2.25×10^{-8} mm Hg at 20 °C (HSDB, 2015)

Flash point: 243 °C (GESTIS, 2015)

Conversion factor: 1 ppm = 6.83 mg/m^3 (HSDB, 2015).

1.2 Production and use

1.2.1 Production

(a) Production process

2-Mercaptobenzothiazole is produced by reacting aniline, carbon disulfide, and sulfur at high temperature and pressure; the product is then purified by dissolution in a base to remove the dissolved organics. Re-precipitation is achieved by the addition of acid (Kirk-Othmer, 1982; NTP, 1988).

(b) Production volume

2-Mercaptobenzothiazole is listed as a chemical with high production volume by the Organisation for Economic Co-operation and Development (OECD, 2004) and in the USA (Federal Register, 2000; HSDB, 2015).

In 2006, the inventory-aggregated national production volume for 2-mercaptobenzothiazole in the USA was between 10 and < 50 million pounds [~4536 to < 22 680 tonnes]. The United States Environmental Protection Agency (EPA) noted that 500 000–1 000 000 pounds/year [~227–454 tonnes/year] of 2-mercaptobenzothiazole were produced, imported, and used in the USA in 2012 (EPA, 2012). In 2012, three facilities in three states were listed as manufacturing 2-mercaptobenzothiazole in the USA (HSDB, 2015).

2-Mercaptobenzothiazole is registered with the European Chemicals Agency, and production was stated to be 1000–10 000 tonnes per year from three manufacturers in three countries, one each in Belgium, Spain, and the United Kingdom (ECHA, 2012).

A commercial website identified a larger number of suppliers: 225 in China, 13 in the USA, five in India, two in Hong Kong Special Administrative Region, and one each in Canada, France, Germany, Japan, the Russian Federation, and Turkey (GuideChem, 2015).

1.2.2 Use

2-Mercaptobenzothiazole is principally used as a reactant in the manufacture of rubber products, but is also used as a corrosion inhibitor in oils, greases and cooling fluids. It is added to polyether polymers as a stabilizer to resist damage by air and ozone, and is a component approved in the USA in some skin medications for dogs (HSDB, 2015).

2-Mercaptobenzothiazole is also used as an intermediate in the production of pesticides such as 2-(thiocyanomethylthio)benzothiazole (Azam & Suresh, 2012), and sodium and zinc salts of 2-mercaptobenzothiazole are approved for use as pesticides by the EPA (1994).

1.3 Measurement and analysis

Several analytical methods are available for the determination of 2-mercaptobenzothiazole in environmental samples (e.g. air, water, and food), in rubber products (e.g. disposable medical gloves), in products that come into contact with rubber materials (e.g. medical drug solutions or industrial coolant solutions), and in the urine of exposed persons (Table 1.1). Generally, the use of stable isotope-labelled surrogate standards is recommended for the specific analysis of 2-mercaptobenzothiazole (Wick et al., 2010). A single method has been described for the determination of 2-mercaptobenzothiazole in dietary products (Barnes et al., 2003).

1.4 Occurrence and exposure

Due to its use as an accelerant in rubber vulcanization, 2-mercaptobenzothiazole can be found as a contaminant in rubber products. Sensitization to 2-mercaptobenzothiazole is common in occupational and non-occupational settings and can be used as an indicator of exposure (HSDB, 2015).

1.4.1 Natural occurrence

2-Mercaptobenzothiazole is not known to occur in nature.

1.4.2 Environmental occurrence

(a) Air

Urban particulate matter was sampled in a street in Stockholm, Sweden, using a device made in-house; average concentrations of 2-mercaptobenzothiazole were 64 pg/m^3 in airborne particulate matter, and 591 pg/m^3 in total suspended particulate matter, and were thought to derive from tyre wear (Avagyan et al., 2014).

Table 1.1 Selected methods of analysis for 2-mercaptobenzothiazole

Sample matrix	Sample preparation	Assay method	Limit of detection	Reference
Air				
Workplace air	Collection on quartz fibre filters; stabilization by covering with double-distilled water; desorption using an ultrasonic bath; filtration of the sample Sampling recommendation: 2 h at 1 L/min (120 L)	CE/DAD	0.2 mg/m^3 [a]	Breuer et al. (2002)
Water				
Municipal and industrial wastewater	Extraction using methylene chloride at pH 6–8; drying and concentrating the sample; change solvent to methanol; if necessary: silica gel column clean-up	HPLC/UV	1.7 µg/L	EPA (1993)
Treated and raw wastewater	Direct injection of the (diluted) effluent samples	HPLC/ESI-MS/MS	0.2 µg/L	Reemtsma (2000)
Treated wastewater and raw municipal wastewater	SPE using a co-polymeric sorbent (divinylbenzene, *N*-vinylpyrrolidone); elution with methanol/acetone; addition of the internal standard; concentration of the eluent	HPLC/ESI-MS	0.05 µg/L 0.12 µg/L	Kloepfer et al. (2004a)
Cooling water (spiked)	Direct analysis of the undiluted samples at pH 8 (buffered)	SWV	0.8 mg/L	Parham et al. (2008)
Cooling water (spiked)	SPE using a cartridge loaded with copper oxide nanoparticles at pH 5–8; washing the sorbent with 0.5 M sodium thiosulfate; desorption of the cartridge using methanol	HPLC/UV	1.9 µg/L	Parham & Khoshnam (2013)
Cooling water and drinking-water (spiked)	Addition of gold nanoparticle solution and citrate buffer (pH 6)	RRS, SFP	1.0 µg/L	Parham et al. (2015)
Food				
Dietary products	Milk, yoghurt, infant formula: addition of an internal standard; protein precipitation by the addition of acetonitrile; sample filtration All other foodstuffs: addition of an internal standard, acetic acid and acetonitrile; sonication of the sample followed by centrifugation and filtering	HPLC/APCI-MS	8–43 µg/kg [b]	Barnes et al. (2003)
Products				
Coolant formulations	Direct analysis of the undiluted samples	HPLC/UV	0.02%	Schmitt & Muzher (1981)
Injectable solutions	Mixing with 1 M hydrochloric acid; extraction with chloroform; evaporation to dryness and reconstitution in acetonitrile	HPLC/UV	NA	Reepmeyer & Juhl (1983)
Protective gloves	Extraction using acetone; evaporation to dryness and reconstitution in acetonitrile; filtration of the sample	HPLC/DAD	1 mg/L	Bergendorff et al. (2006)

Table 1.1 (continued)

Sample matrix	Sample preparation	Assay method	Limit of detection	Reference
Urine				
Experimental animals	Acidic hydrolysis using 5 M sulfuric acid; incubation at room temperature; SPE using C_{18} cartridges; elution with ethyl acetate; evaporation to dryness and reconstitution in ethanol	GC/MS	20 µg/L	Manninen et al. (1996)
Exposed workers and non-exposed controls	Homogenization and addition of ammonium acetate buffer (pH 6.5), deuterated internal standard (MBT-d_4) and β-glucuronidase/arylsulfatase; homogenization of the samples, incubation overnight at 37 °C and centrifugation	HPLC/ESI-MS/MS	0.4 µg/L	Gries et al. (2015)

[a] The analysis is considered to be semi-quantitative. The coefficient of variation of the calibration is 1.8%, therefore the analytical procedure itself is precise; however, due to the instability of 2-mercaptobenzothiazole on the filter, large overall variation can occur (up to 16% depending on the concentration)

[b] Depending on the food

APCI, atmospheric pressure chemical ionization; CE, capillary electrophoresis; DAD, diode array detection; ESI, electrospray ionization; GC, gas chromatography; HPLC, high-performance liquid chromatography; MBT, 2-mercaptobenzothiazole; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NA, not available; RRS, resonance Raleigh scattering; SFP, spectrofluorophotometry; SPE, solid-phase extraction; SWV, square wave voltammetry; UV, ultraviolet detection *(b) Water*

Effluent from a waste dump was analysed for 2-mercaptobenzothiazole by liquid chromatography in a study aimed at developing analytical methods; the concentration of 2-mercaptobenzothiazole was estimated at 30 μg/L in the sample tested (Cox, 1976).

A study of municipal wastewater in Germany found 2-mercaptobenzothiazole at a concentration of up to 0.19 μg/L (Kloepfer et al., 2004b). In a comprehensive survey of wastewater from 4000 industrial and publicly owned treatment works sponsored by the Effluent Guidelines Division of the EPA, 2-mercaptobenzothiazole was identified in one discharge each from a rubber-processing and pesticide-manufacturing industry at a concentration of 1.27 ppm [8.67 μg/L] and 0.86 ppm [5.87 μg/L], respectively (Shackelford et al., 1983). The mean concentration of 2-mercaptobenzothiazole in the effluent from a paper mill was 0.025 ppm [0.17 μg/L] (Keith, 1976), and a concentration of 30 μg/L was found in the wastewater from a tyre-manufacturing plant (Jungclaus et al., 1976). 2-Mercaptobenzothiazole has been detected in tannery wastewater at concentrations ranging from 420 to 840 μg/L (Rodríguez et al., 2004), and in trace amounts in natural surface-water samples as a degradation product of the wood preservative 2-(thiocyanomethylthio)benzothiazole, which leaked from an upstream sawmill (Khoroshko et al., 2005).

(c) Products

(i) Medical devices

An investigation of adverse reactions to an excretory urography contrast agent detected 2-mercaptobenzothiazole at concentrations of up to 3.3 μg/mL. At this concentration, a dose of the contrast agent of 100 mL would contain 0.33 mg of 2-mercaptobenzothiazole (Hamilton, 1987).

Leaching of 2-mercaptobenzothiazole into drug preparations of several constituents of elastomeric closures was assessed. In syringe cartridges, concentrations of 2-mercaptobenzothiazole ranged from 8.3 to 13.8 μg/mL (Airaudo et al., 1990).

An investigation of instability of a therapeutic protein for infusion revealed that 2-mercaptobenzothiazole and its zinc salt leached from the stopper used for the infusion bags (100 mL) (Chang et al., 2010).

(ii) Consumer products

A survey of 19 rubber gloves found that two contained 2-mercaptobenzothiazole (5–8 μg/g) (Bergendorff et al., 2006).

In 2001, a retail market survey of 19 samples of baby bottle teats and soothers was performed in the Netherlands. The migration of 2-mercaptobenzothiazole was detected in only one natural rubber sample, and was considerably lower than the limit of 0.3 mg/teat (Bouma et al., 2003).

In the United Kingdom, in 2000, 2-mercaptobenzothiazole was not detected in 236 retail samples of food that may have been in contact with rubber material during their fabrication, transport, or storage (Barnes et al., 2003).

1.4.3 Occupational exposure

2-Mercaptobenzothiazole has been detected in the urine samples of four workers employed at a plant producing 2-mercaptobenzothiazole, one worker from the administration department of the plant, and only one out of forty persons not knowingly exposed to 2-mercaptobenzothiazole (Gries et al., 2015). Mean concentrations of 2-mercaptobenzothiazole in the four exposed workers were 3958 μg/L after enzymatic hydrolysis of the urine sample during sample preparation; without hydrolysis, the concentration determined was only 69 μg/L. The results showed that most 2-mercaptobenzothiazole in the urine was excreted in conjugated forms (e.g.

2-mercaptobenzothiazole glucuronide) rather than in its unchanged form. Using this method (with hydrolysis), 2-mercaptobenzothiazole was detected in only one (11 µg/L) out of the 40 samples of urine collected from non-exposed individuals. The person from the administration department excreted 2-mercaptobenzothiazole at 2.5 µg/L and was thus within the range for non-exposed individuals.

The data from all employed patients (age range, 16–68 years; *n* = 14 234) patch-tested between 2003 and 2013 in the German Information Network of Departments of Dermatology, and diagnosed as having occupationally acquired contact dermatitis were analysed. The control group comprised all other patients (*n* = 31 706) within the same time frame who tested negative for occupationally acquired allergic contact dermatitis. The prevalence ratio (indicating risk) was significantly increased for 2-mercaptobenzothiazole (prevalence ratio, 3.88; 95% confidence interval [CI], 3.09–4.89) (Bauer et al., 2015).

A series of 23 patients with allergic contact dermatitis (some with disseminated dermatitis) due to rubber accelerators in rubber gloves treated during a 2-year period was described. Sixteen were health-care workers from a single institution whose dermatitis was temporally related to the switch to latex-safe gloves. Each had positive patch-test reactions to one or more rubber accelerators, including 2-mercaptobenzothiazole. Chemical analysis identified 2-mercaptobenzothiazole in four out of six glove samples (Cao et al., 2010).

A retrospective analysis of data from the Information Network of Departments of Dermatology in 2002–10 found that, of 93 615 patients who were patch tested, 3448 had occupational dermatitis and were tested because of a suspected glove allergy. Of all the occupational dermatitis patients, 3% were sensitized to 2-mercaptobenzothiazole and/or its derivatives (Geier et al., 2012).

Standard patch test results of employed persons with an initial report of an occupational skin disease were analysed within 24 occupational groups. Among the occupationally relevant sensitizers, mercapto-mix/mercaptobenzothiazole contributed to 35% of the positive results (Dickel et al., 2002).

1.4.4 Exposure of the general population

Case reports that included a patch test confirmed that contact with 2-mercaptobenzothiazole was from a foley catheter (Ancona et al., 1985), a rubber earplug (Deguchi & Tagami, 1996), safety shoes (Foussereau et al., 1986), rubber gloves (Geier et al., 2012), a condom catheter (Harmon et al., 1995), and a bikini with rubberized elastic (Jung et al., 2006).

A total of 155 cases with footwear dermatitis were evaluated from July 2005 to June 2006 from detailed histories, clinical examinations, and patch testing. Contributory allergens included 2-mercaptobenzothiazole (12.9%; *n* = 20) (Chowdhuri & Ghosh, 2007).

In a study of dermatitis among athletes, 43 young adults (31 men and 12 women) with eczematous skin lesions suggesting allergic contact dermatitis were patch-tested; 21% tested positive for 2-mercaptobenzothiazole (Ventura et al., 2001).

Investigators in Spain used gas chromatography–mass spectrometry to analyse the 2-mercaptobenzothiazole content of samples of crumb rubber from urban playgrounds and from rubber pavers. Ten of the 21 samples from playgrounds contained quantifiable 2-mercaptobenzothiazole (mean, 195 µg/g; median, 185 µg/g; maximum, 398 µg/g). No 2-mercaptobenzothiazole was detected in the nine samples from rubber pavers analysed (Llompart et al., 2013).

1.4.5 *Exposure assessment in epidemiological studies*

Strauss et al. (1993) studied a production facility in West Virginia, USA, where 2-mercaptobenzothiazole had been produced since 1934. A former plant industrial hygienist developed annual airborne exposure estimates throughout the study period for all hourly production jobs, using sampling data available from 1977 to 1989, historical company documents, and interviews with knowledgeable retirees for the period before 1977. Jobs with potential exposure to 2-mercaptobenzothiazole were assigned to four exposure categories: very low (> 0–0.5 mg/m^3), low (> 0.5–2.0 mg/m^3), medium (> 2.0–5.0 mg/m^3) and high (> 5.0–20.0 mg/m^3). Jobs in these categories were not named. A cumulative exposure index for each job was calculated by multiplying the midpoint of each exposure category by duration in a 2-mercaptobenzothiazole-exposed job. Three categories of cumulative exposure to 2-mercaptobenzothiazole were calculated: < 2 mg/m^3–year (46% of the cohort), 2–7 mg/m3–year (32% of the cohort), and 8–129 mg/m^3–year (22% of the cohort). No description of the processes was included in the report, therefore no information on exposure characteristics by process could be derived. Collins et al. (1999) extended the follow-up of this cohort and noted that, in 1943–54, average exposures generally exceeded 2 mg/m^3. Again, no information on the processes was provided.

A mortality study was conducted among employees at a plant in Wales, United Kingdom, that had manufactured 2-mercaptobenzothiazole since 1932 and other chemicals, including *ortho*-toluidine, aniline, phenyl-β-naphthylamine, and polymerized 2,2,4-trimethyl-1,2-dihydroquinoline. A former occupational hygienist from the plant provided assessments of 8-hour time-weighted average (TWA) exposures to both 2-mercaptobenzothiazole and its derivatives over a range of years and for each job and department title. Various jobs entailed either zero exposure, very low (0–1 mg/m^3), low (1–2.5 mg/m^3), medium (2.5–6 mg/m^3) or high (6–20 mg/m^3) exposure. Estimates were made on the basis of monitoring data from 1977 onwards, a review of process manuals and other company records for earlier years, and discussions with long-serving employees. Annual exposure estimate were adjusted by a “year fraction” factor per job, to take into account the duration of exposure for a working year. Cumulative exposure strata were reported as none, 0.01–21.24 mg/m^3–year, 21.25–63.74 mg/m^3–year, and ≥ 63.75 mg/m^3–year. No description of the processes was supplied and no exposures by process or distribution of workers by exposure strata were reported (Sorahan & Pope, 1993). A second report on this cohort provided further details of the matrix of exposure levels by job title and year. The highest exposures were 11.7 mg/m^3 for day pack and pellet operators, and 8.5 mg/m^3 for bag flake operators and daymen. The same cumulative exposure strata were reported (Sorahan et al., 2000). A third update (Sorahan, 2008) and a fourth update (Sorahan, 2009) of this cohort used the same exposure assessment. [The Working Group noted that exposure to 2-mercaptobenzothiazole dust would be associated with jobs identified within the compounding area or described as batch preparation. Downstream, skin contact with expressed 2-mercaptobenzothiazole and absorption would be higher in jobs before curing (green rubber), such as milling, calendaring, and tyre building, although there may still be skin absorption from cured rubber.]

1.5 Regulations and guidelines

The legal occupational exposure in Germany for 2-mercaptobenzothiazole is 4 mg/m^3 inhalable dust. No other permissible limits were found (GESTIS, 2015).

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) designation of 2-mercaptobenzothiazole is H317, “may cause an allergic skin reaction” and H410 “very toxic to aquatic life with long-lasting effects” (ECHA, 2015).

2. Cancer in Humans

See Table 2.1

A series of studies of workers at a chemical production plant in north Wales, United Kingdom, provided most of the pertinent evidence pertaining to associations between occupational exposure to 2-mercaptobenzothiazole and cancer (Sorahan & Pope, 1993; Sorahan et al., 2000; Sorahan, 2008, 2009). Some workers in the plant were also exposed to other chemicals (aniline, phenyl-β-naphthylamine, *ortho*-toluidine, and polymerized 2,2,4-trimethyl-1,2-dihydroquinoline) (Sorahan et al., 2000).

Within a cohort of 2160 male production workers employed for at least 6 months and with some employment during 1955–84, 363 were exposed to 2-mercaptobenzothiazole, 94 were exposed to phenyl-β-naphthylamine, 53 were exposed to *ortho*-toluidine, and 442 were exposed to aniline, but overlaps among the exposed groups were not specified (Sorahan, 2008). Sorahan (2008) focused on morbidity and mortality from cancer of the urinary bladder in the cohort exposed to 2-mercaptobenzothiazole and found an excess in mortality (8 deaths; standardized mortality ratio [SMR], 3.74; 95% CI, 1.62–7.37) and incidence (12 cases; standardized relative risk [SRR], 2.53; 95% CI, 1.31–4.41) compared with national rates (population of England and Wales). In an internal multivariate analysis of incident bladder cancer using the full cohort and adjusting for age, calendar period, and duration of employment with exposure to *ortho*-toluidine, aniline, and phenyl-β-naphthylamine, a positive non-significant trend ($P = 0.16$) was found with cumulative exposure to 2-mercaptobenzothiazole (0.01–21.24 mg/m^3–year: 6 cases; relative risk [RR], 0.97; 95% CI, 0.38–2.43; 21.25–63.74 mg/m^3–year: 6 cases; RR, 1.70; 95% CI, 0.65–4.41; ≥ 63.75 mg/m^3–year: 3 cases; RR, 2.12; 95% CI, 0.64–7.06). The 15 cases in the three exposed groups included three with benign or in-situ tumours.

A subsequent report that presented data on the mortality from and incidence of cancers other than those of the urinary bladder among male workers exposed to 2-mercaptobenzothiazole relative to unexposed workers found excesses for cancers of the large intestine, lung and multiple myeloma (Sorahan, 2009). In the subcohort exposed to 2-mercaptobenzothiazole, there were eight deaths (SMR, 2.32; 95% CI, 1.00–4.57) from and nine diagnoses (SRR, 1.81; 95% CI, 0.83–3.44) of cancer of the large intestine, 27 deaths (SMR, 1.38; 95% CI, 0.91–2.01) from and 26 diagnoses (SRR, 1.52; 95% CI, 0.99–2.23) of lung cancer, and three deaths (SMR, 4.40; 95% CI, 0.91–12.87) from and four diagnoses (SRR, 4.65; 95% CI, 1.27–11.91) of multiple myeloma. In internal multivariate analyses of incidence in the full cohort that adjusted for the duration of employment with exposure to *ortho*-toluidine, aniline and phenyl-β-naphthylamine, significant trends of increased incidence with increased cumulative exposure to 2-mercaptobenzothiazole remained for cancer of the large intestine ($P < 0.001$) and multiple myeloma ($P = 0.019$). [The trend analysis for multiple myeloma was based on small numbers (4 exposed cases).]

Collins et al. (1999) studied a cohort of 1059 male chemical-production workers in Nitro, West Virginia, USA, exposed to 2-mercaptobenzothiazole and 4-aminobiphenyl (classified in IARC Group 1 as a cause of cancer of the urinary bladder) in an update of a report by Strauss et al. (1993). Among 511 2-mercaptobenzothiazole workers with no documented exposure to 4-aminobiphenyl, five deaths from urinary bladder cancer (SMR, 4.3; 95% CI, 1.4–10.0)

Table 2.1 Cohort studies of cancer and exposure to 2-mercaptobenzothiazole

Reference, location, enrolment/ follow-up period	Population size, description; method of exposure assessment	Organ site	Exposure category or level	No. of exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Collins et al. (1999) Nitro, WV, USA 1955–77	1059 (600 with MBT exposure), white male production workers active for ≥ 1 day; JEM Social Security Administration, National Death Index, motor vehicle bureau, credit records	All cancers combined	Total MBT cohort	63	1.0 (0.8–1.3)	NR	Strengths: extended follow-up Limitations: sampling data from 1977–89 only; no data on cigarette smoking
			Job involving MBT with 4-ABP	23	2.0 (1.3–3.0)		
			Job involving MBT without 4-ABP	40	0.8 (0.5–1.0)		
		Lung	Total MBT cohort	27	1.0 (0.7–1.5)	NR	
			Job involving MBT with 4-ABP	11	2.4 (1.2–4.3)		
			Job involving MBT without 4-ABP	16	0.7 (0.4–1.2)		
		Prostate	Total MBT cohort	4	0.9 (0.2–2.3)	NR	
			Job involving MBT without 4-ABP	4	1.1 (0.3–2.9)		
		Urinary bladder	Total MBT cohort	13	8.9 (4.7–15.2)	NR	
			Job involving MBT with 4-ABP	8	27.1 (11.7–53.4)		
			Job involving MBT without 4-ABP	5	4.3 (1.4–10.0)		
			Unexposed to MBT or 4-ABP	1	1.2 (0.0–6.5)		
			Cumulative exposure, < 2 mg/m^3-year, no 4-ABP	0	0.0 (0.0–13.8)		
			Cumulative exposure, 2–7.9 mg/m^3-year, no 4-ABP	1	3.5 (0.1–19.5)		
			Cumulative exposure, 8–129 mg/m^3-year, no 4-ABP	4	6.5 (1.8–16.6)		
			Trend test *P*-value: 0.04				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description; method of exposure assessment	Organ site	Exposure category or level	No. of exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sorahan (2008) North Wales, UK 1955–2005	2160 men, hourly staff working for ≥ 6 mo; 8-h TWA to MBT, MBT derivatives, by job and department: zero, very low (0–1 mg/m³), low (1–2.5 mg/m³), medium (2.5–6 mg/m³), high (6–20 mg/m³) 363 men exposed to MBT, 94 men exposed to PBN, 442 men exposed to aniline, 53 men exposed to *ortho*-toluidine) Office of National Statistics	Urinary bladder	0	41	1.00	Duration of employment in departments with exposure to PBN, aniline and *ortho*-toluidine	Trend analysis included benign or in-situ tumours. Strengths: long follow-up, little loss to follow-up Limitations: levels estimated based on monitoring data ≥ 1977, 266 workers in > 1 subcohort, 8 workers in all 4 subcohorts, cancer morbidity data only from 1971 to 2005
			0.01–21.24 mg/m³-year (RR)	6	0.97 (0.38–2.43)		
			21.25–63.74 mg/m³-year (RR)	6	1.70 (0.65–4.41)		
			≥ 63.75 mg/m³-year (RR)	3	2.12 (0.64–7.06)		
			Trend test *P*-value: 0.16				
			SMR	8	3.74 (1.62–7.37)	Age, sex, and period	
			SRR	12	2.53 (1.31–4.41)	Age, sex, and period	
Sorahan (2009) North Wales, UK 1955–2005	2160 men (363 in MBT subcohort), hourly staff working ≥ 6 mo and some employment 1955–84; 8-h TWA to MBT, MBT derivatives, by job and department: zero, very low (0.1–1 mg/m³), low (1–2.5 mg/m³), medium (2.5–6 mg/m³) and high (6–20 mg/m³) Office of National Statistics	Colon: large intestine	SMR	8	2.32 (1.00–4.57)	Duration of employment in departments with exposure to PBN, aniline, and *ortho*-toluidine	Cases represent incidence and include death certificate notifications. Report focused on MBT and adjusted for other chemical exposures Strengths: long follow-up, little loss to follow-up Limitations: levels estimated based on monitoring data ≥ 1977, most workers exposed to > 1 chemical
			SRR	9	1.81 (0.83–3.44)		
			Cumulative exposure, 0 (RR)	27	1.00		
			Cumulative exposure, 0.01–21.24 mg/m³-year (RR)	3	1.24 (0.36–4.26)		
			Cumulative exposure, 21.25–63.74 mg/m³-year (RR)	6	4.76 (1.82–12.43)		

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description; method of exposure assessment	Organ site	Exposure category or level	No. of exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sorahan (2009) North Wales, UK 1955–2005 (cont.)			Cumulative exposure, > 63.75 mg/m³-year (RR)	3	4.69 (1.38–15.90)		
			Trend test *P*-value: < 0.001				
		Lung	SMR	27	1.38 (0.91–2.01)	Duration of employment in departments with exposure to PBN, aniline and *ortho*-toluidine	
			SRR	26	1.52 (0.99–2.23)		
			Cumulative exposure, 0 (RR)	107	1.00		
			Cumulative exposure, 0.01–21.24 mg/m³-year (RR)	21	2.17 (1.30–3.61)		
			Cumulative exposure, 21.25–63.74 mg/m³-year (RR)	4	0.65 (0.23–1.81)		
			Cumulative exposure, ≥ 63.75 mg/m³-year (RR)	4	1.44 (0.53–3.96)		
			Trend test *P*-value: 0.38				

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description; method of exposure assessment	Organ site	Exposure category or level	No. of exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sorahan (2009) North Wales, UK 1955–2005 (cont.)		Multiple myeloma	SMR	3	4.40 (0.91–12.87)	Duration of employment in departments with exposure to PBN, aniline and *ortho*-toluidine	
			SRR	4	4.65 (1.27–11.91)		
			Cumulative exposure, 0 (RR)	2	1.00		
			Cumulative exposure, 0.01–21.24 mg/m^3-year (RR)	2	10.21 (1.27–81.7)		
			Cumulative exposure, 21.25–63.74 mg/m^3-year (RR)	2	20.57 (2.58–164.00)		
			Trend test *P*-value: 0.019				
		All cancers combined	SMR	76	1.41 (1.11–1.77)	NR	
			SRR	97	1.48 (1.20–1.81)		

4-ABP, 4-aminobiphenyl; CI, confidence interval; JEM, job–exposure matrix; MBT, 2-mercaptobenzothiazole; mo, month; NR, not reported; PBN, phenyl-β-naphthylamine; RR, relative risk; SMR, standardized mortality ratio; SRR, standardized relative risk; TWA, time-weighted average occurred. The standardized mortality ratios for bladder cancer in this cohort also showed a statistically significant increasing trend with increasing cumulative exposure to 2-mercaptobenzothiazole (*P* for trend = 0.04). No excess or trend was reported for lung cancer overall, or among workers exposed only to 2-mercaptobenzothiazole; however, the SMR for workers also exposed to 4-aminobiphenyl was elevated (SMR, 2.4; 95% CI, 1.2–4.3). No findings were presented for multiple myeloma or colon cancer in the cohort exposed to 2-mercaptobenzothiazole.

The use of 2-mercaptobenzothiazole was mentioned in studies conducted at another rubber chemical plant by the United States National Institute for Occupational Safety and Health (NIOSH), but results for urinary bladder cancer were only given for exposure to *ortho*-toluidine (NIOSH, 1989, 1992; Carreón et al., 2014).

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

Oral administration

Groups of 18 male and 18 female B6C3F$_1$ and C57BL/6 × AKR mice (age, 7 days) received 2-mercaptobenzothiazole [purity not reported; "commercial product" Captax] at a dose of 0 (control) or 100 mg/kg body weight (bw) in 0.5% gelatin daily by gavage for 3 weeks, followed immediately by continuous treatment with diets containing 2-mercaptobenzothiazole at a concentration of 0 (control) or 323 ppm for up to 18 months. [These dose rates were considered to be the maximal tolerated dose based on short-term studies of dose-related mortality.] Control mice were housed in the same room. At 18 months, mice were subjected to a post-mortem evaluation of the major thoracic and abdominal organs and the thyroid, but the cranium was not dissected. Results were characterized as the incidence of hepatoma, pulmonary tumours, and lymphoma, and the total number of mice with tumours. Statistical analyses compared treated mice by sex and strain combination with five pooled negative-control groups using the Mantel-Haenszel procedure for the combined relative risk, using the weighted geometric mean with the ½ correction. Under the conditions of this study, administration of 2-mercaptobenzothiazole did not cause a significant increase in the incidence of tumours (Innes et al., 1969). [The limitations of this single-dose study were the small number of animals per group and the inadequate reporting of results, including the lack of information on survival, and the limited macroscopic and microscopic post-mortem evaluation. The Working Group considered this study to be inadequate for an evaluation of the carcinogenicity of 2-mercaptobenzothiazole.]

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 8 weeks) were given 2-mercaptobenzothiazole (purity, 96.3%) at a dose of 0, 375, or 750 mg/kg bw by gavage in corn oil on 5 days per week for 103 weeks. Survival was significantly decreased in female mice at 750 mg/kg bw. In male mice, mean body weights were 6–14% lower in those at 750 mg/kg bw, and 4–8% lower in those at 375 mg/kg bw, compared with controls. In female mice, mean body weights in the group at 750 mg/kg bw were within 6% of the level in vehicle controls, while those of the group at 375 mg/kg bw were generally greater than the level in vehicle controls.

In female mice, treatment with 2-mercaptobenzothiazole resulted in an increase in the incidence of hepatocellular adenoma or carcinoma (combined) only at 375 mg/kg bw (4/50 [adjusted rate, 10.8%] controls; 12/49 [adjusted rate, 29.8%] at 375 mg/kg bw (*P* = 0.035 by the pairwise life-table test, *P* = 0.028 by pairwise incidental-tumour test) and 4/50 [adjusted rate, 18.2%] at 750 mg/kg bw). The historical incidence of

Table 3.1 Studies of carcinogenicity in experimental animals given 2-mercaptobenzothiazole by oral administration

Species, strain (sex) Age at start Duration Reference	Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M+F, combined) 7 days 18 mo Innes et al. (1969)[a]	Commercial product, "Captax" 0.5% gelatin (gavage) 0, 323 ppm Daily on days 7–35 (100 mg/kg bw), in the diet (0 or 323 ppm) for remainder 36/group 32, NR	Hepatomas, pulmonary tumours and lymphoma: NR	NS	Groups of 18 male and 18 female animals at start of study; the authors reported no significant increase in the incidence of hepatomas, pulmonary tumours, lymphoma or total tumours in treated mice
Mouse, C57BL/6 × AKR (M+F, combined) 7 days 18 mo Innes et al. (1969)[a]	Commercial product, "Captax" 0.5% gelatin (gavage) 0, 323 ppm Daily gavage on days 7–35 (100 mg/kg bw), in the diet (0 or 323 ppm) for remainder 36/group 33, NR	Hepatomas, pulmonary tumours and lymphoma: NR	NS	Groups of 18 male and 18 female animals at start of study; the authors reported no significant increase in the incidence of hepatomas, pulmonary tumours, lymphoma or total tumours in treated mice
Mouse, B6C3F$_1$ (M) 8 wks 103 wks NTP (1988)[b]	Purity, 96.3% Corn oil 0, 375, 750 mg/kg bw by gavage 5 days/wk 50/group 38, 33, 30	Any tumour type	NS	No evidence of carcinogenicity
Mouse, B6C3F$_1$ (F) 8 wks 103 wks NTP (1988)[b]	Purity, 96.3% Corn oil 0, 375, 750 mg/kg bw 5 days/wk 50/group 37, 39, 22	*Liver* Hepatocellular adenoma: 3/50, 7/49, 4/50 Hepatocellular carcinoma: 1/50, 5/49, 0/50 Hepatocellular adenoma or carcinoma (combined): 4/50, 12/49, 4/50	 NS NS 375 mg/kg: pairwise $P = 0.035$ (life-table test), $P = 0.028$ (incidental-tumour test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344 (M) 6–7 wks 103 wks NTP (1988)[b]	Purity, 96.3% Corn oil 0, 375, 750 mg/kg bw by gavage 5 days/wk 50/group 42, 22, 20	*Adrenal gland* Pheochromocytoma, benign or malignant: 18/50, 27/50, 24/49	Trend, $P < 0.001$ (life-table test, $P = 0.038$ (incidental-tumour test); 375 mg/kg: pairwise $P < 0.001$ (life-table test), $P = 0.021$ (incidental-tumour test); 750 mg/kg: pairwise $P < 0.001$ (life-table test, $P = 0.034$ (incidental-tumour test).	
		Pheochromocytoma, benign: 18/50, 25/50, 22/49	Trend, $P = 0.002$ (life-table test); 375 mg/kg: pairwise $P < 0.001$ (life-table test); 750 mg/kg: pairwise $P = 0.002$ (life-table test)	
		Pheochromocytoma, malignant: 0/50, 2/50, 2/49	NS	
		Haematopoietic system Mononuclear cell leukaemia: 7/50, 16/50, 3/50	375 mg/kg: pairwise $P = 0.002$ (life-table test)	
		Pancreas Acinar cell adenoma: 2/50, 13/50, 6/49	Trend, $P = 0.017$ (life-table test); 375 mg/kg: pairwise $P < 0.001$ (life-table test), $P < 0.001$ (incidental-tumour test); 750 mg/kg: pairwise $P = 0.030$ (life-table test)	
		Mesothelium Mesothelioma (multiple organs): 0/50, 2/50, 3/50	Trend, $P = 0.039$ (life-table test), $P = 0.041$ (incidental-tumour test); historical corn oil vehicle controls NTP studies: 55/1450 (4% ± 3%); range, 0–6/50	
		Preputial gland Adenoma or carcinoma (combined): 1/50, 6/50, 5/50	Trend, $P = 0.027$ (life-table test); 375 mg/kg: pairwise $P = 0.021$ (life-table test); 750 mg/kg: pairwise $P = 0.030$ (life-table test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344 (M) 6–7 wks 103 wks NTP (1988)[b] (cont.)		Adenoma: 0/50, 4/50, 4/50	Trend, $P = 0.016$ (life-table test), $P = 0.042$ (incidental-tumour test); 375 mg/kg: pairwise $P = 0.019$ (life-table test); 750 mg/kg: pairwise $P = 0.021$ (life-table test)	
		Carcinoma: 1/50, 2/50, 1/50	NS	
		Pituitary gland		
		Adenoma: 14/50, 21/50, 12/48	375 mg/kg: pairwise $P = 0.003$ (life-table test)	
		Skin, subcutaneous		
		Fibroma, neurofibroma, sarcoma, or fibrosarcoma (combined): 3/50, 6/50, 7/50	Trend, $P = 0.031$ (life-table test); 750 mg/kg: pairwise $P = 0.037$ (life-table test); historical controls, corn oil vehicle, NTP studies: 126/1450 (9% ± 4%)	
Rat, F344 (F) 6–7 wks 103 wks NTP (1988)[b]	Purity, 96.3% Corn oil 0, 188, 375 mg/kg bw by gavage 5 days/wk 50/group 28, 31, 25	*Adrenal gland*		
		Pheochromocytoma (benign): 1/50, 5/50, 6/50	Trend, $P = 0.030$ (life-table test), $P = 0.038$ (incidental-tumour test); 750 mg/kg: pairwise $P = 0.041$ (life-table test)	
		Pituitary gland		
		Adenoma: 15/49, 24/50, 25/50	Trend, $P = 0.014$ (life-table test), $P = 0.015$ (incidental-tumour test); 375 mg/kg: pairwise $P = 0.021$ (life-table test), $P = 0.027$ (incidental-tumour test)	
		Adenoma or adenocarcinoma (combined):16/49, 24/50, 25/50	Trend, $P = 0.024$ (life-table test,) $P = 0.028$ (incidental-tumour test); 375 mg/kg: pairwise $P = 0.036$ (life-table test); 1 (control) animal had a pituitary gland adenocarcinoma	

[a] Principal limitations of the study: inadequate reporting of results, limited macroscopic and microscopic evaluation, purity not reported and single dose tested
[b] Principal strengths of the study: good laboratory practice, covers most of the lifespan, multiple doses tested and large number of animals per group
bw, body weight; F, female; M, male; mo, month; NR, not reported; NS, not significant; NTP, United States National Toxicology Program; wk, week

hepatocellular adenoma or carcinoma (combined) among female control mice in studies conducted by the National Toxicology Program (NTP) cited in the report was 116/1489 (8% ± 6%). The incidence of hepatocellular adenoma and hepatocellular carcinoma was 3/50 and 1/50 in the control group, 7/49 and 5/49 in the group at 375 mg/kg bw, and 4/50 and 0/50 at 750 mg/kg bw, respectively. In male mice, treatment with 2-mercaptobenzothiazole did not result in significant increases in tumour incidence, unusual tumours or early-onset tumours (NTP, 1988). [The strengths of this study included the large numbers of animals, compliance with good laboratory practice, the evaluation of multiple dose levels, and the duration of exposure that involved most of the lifespan.]

3.2 Rat

Oral administration

Groups of 50 male and 50 female Fischer 344/N rats (age, 6–7 weeks) were given 2-mercaptobenzothiazole (purity, 96.3%) at a dose of 0, 188 (females only), 375, or 750 (males only) mg/kg bw daily by gavage in corn oil on 5 days per week for 103 weeks. Survival was significantly decreased in male rats at 375 or 750 mg/kg bw. The mean body weights of treated males were similar to or greater than those of control males, and those of treated females were greater than those of control females.

In male rats, treatment with 2-mercaptobenzothiazole resulted in an increase in the incidence of pheochromocytoma of the adrenal gland (benign or malignant, combined) in the groups at 375 and 750 mg/kg bw: 18/50 controls, 27/50 at 375 mg/kg bw ($P < 0.001$ by the pairwise life-table test, $P = 0.021$ by the pairwise incidental-tumour test), and 24/49 at 750 mg/kg bw ($P < 0.001$ by the pairwise life-table test, $P = 0.034$ by the pairwise incidental-tumour test). Statistical analyses detected a positive dose-related trend using the life-table ($P < 0.001$) and incidental-tumour ($P = 0.038$) tests. The reported historical incidence of benign or malignant pheochromocytoma (combined) in male control rats was 347/1442 (24% ± 9%). In addition, an increase in the incidence of benign pheochromocytoma was observed in treated males: 18/50 controls, 25/50 at 375 mg/kg bw ($P < 0.001$ by the pairwise life-table test), and 22/49 at 750 mg/kg bw ($P = 0.002$ by the pairwise life-table test). Statistical analyses detected a positive dose-related trend using the life-table test ($P = 0.002$). The incidence of malignant pheochromocytoma was 0/50 controls, 2/50 at 375 mg/kg bw, and 2/49 at 750 mg/kg bw. An increase in the incidence of mononuclear cell leukaemia of the haematopoietic system was also observed in the group at 375 mg/kg bw only (7/50 controls, 16/50 at 375 mg/kg bw ($P = 0.002$ by the pairwise life-table test) and 3/50 at 750 mg/kg bw). The reported historical incidence of mononuclear cell leukaemia in male control rats was 202/1450 (14% ± 8%). The incidence of pancreatic acinar cell adenoma was increased in treated males (2/50 controls, 13/50 at 375 mg/kg bw ($P < 0.001$ by the pairwise life-table test, $P < 0.001$ by the pairwise incidental-tumour test), and 6/49 at 750 mg/kg bw ($P = 0.030$ by the pairwise life-table test)). Statistical analyses detected a positive dose-related trend using the life-table test ($P = 0.017$), and the reported historical incidence of pancreatic acinar cell neoplasms in male control rats was 80/1381 (6% ± 8%). The incidence of preputial gland adenoma or carcinoma (combined) was also increased in treated males (1/50 controls, 6/50 at 375 mg/kg bw ($P = 0.021$ by the pairwise life-table test), and 5/50 at 750 mg/kg bw ($P = 0.030$ by the pairwise life-table test)). Statistical analyses detected a positive dose-related trend using the life-table test ($P = 0.027$), and the reported historical incidence of preputial gland adenoma or carcinoma (combined) in male control rats was 65/1450 (4% ± 4%). In addition, the treatment resulted in an increase in the incidence of preputial gland adenoma in males: 0/50 controls, 4/50 at 375 mg/kg bw (*P* = 0.019 by the pairwise life-table test), and 4/50 at 750 mg/kg bw (*P* = 0.021 by the pairwise life-table test). Statistical analyses detected a positive dose-related trend using the life-table (*P* = 0.016) and incidental tumour (*P* = 0.042) tests, but did not detect a positive dose-related trend or increases in the incidence of preputial gland carcinoma in individual treatment groups (1/50 controls, 2/50 at 375 mg/kg bw, and 1/50 at 750 mg/kg bw) using either the life-table or incidental-tumour tests. The reported historical incidence of carcinoma of the preputial gland in male control rats was 35/1450 (2% ± 3%). A significant positive trend (*P* = 0.041 by the incidental-tumour test, *P* = 0.039 by the life-table test) in the incidence of mesothelioma (multiple organs) was observed (0/50 controls, 2/50 at 375 mg/kg bw, and 3/50 at 750 mg/kg bw). This increase was not statistically significant by pairwise comparison for either of the treated groups, and the incidence did not exceed that of historical corn-oil vehicle controls (55/1450, 4% ± 3%; reported range, 0–6/50). Also, an increase in the incidence of tumours of the skin (fibroma, neurofibroma, sarcoma, or fibrosarcoma combined) was observed in treated males (3/50 controls, 6/50 at 375 mg/kg bw, and 7/50 at 750 mg/kg bw (*P* = 0.037 by the pairwise life-table test)), and was associated with a significant positive trend (*P* = 0.031 by the life-table test). The incidence of adenoma of the pituitary gland was increased only at a dose of 375 mg/kg bw (14/50 controls, 21/50 at 375 mg/kg bw (*P* = 0.003 by the pairwise life-table test), and 12/48 at 750 mg/kg bw) with a reported historical incidence of 344/1411 (24% ± 8%).

In female rats, treatment with 2-mercaptobenzothiazole resulted in an increase in the incidence of benign pheochromocytoma of the adrenal gland only at a dose of 375 mg/kg bw (1/50 controls, 5/50 at 188 mg/kg bw, and 6/50 at 375 mg/kg bw (*P* = 0.041 by the pairwise life-table test)). Statistical analyses detected a positive dose-related trend using the life-table test (*P* = 0.030) and the incidental-tumour test (*P* = 0.038), and the reported historical incidence of benign pheochromocytoma in female controls was 82/1443 (6% ± 4%). An increase in the incidence of adenoma of the pituitary gland was also observed in females at 375 mg/kg bw (15/49 controls, 24/50 at 188 mg/kg bw, and 25/50 at 375 mg/kg bw (*P* = 0.021 by the pairwise life-table test, *P* = 0.027 by the pairwise incidental-tumour test)). Statistical analyses detected a positive dose-related trend using the life-table (*P* = 0.014) and incidental-tumour (*P* = 0.015) tests. One rat in the control group had a pituitary adenocarcinoma. The reported historical incidence of adenoma, carcinoma, or adenocarcinoma (combined) of the pituitary gland in female control rats was 561/1407 (40% ± 8%) (NTP, 1988). [The strengths of this study included the large numbers of animals, compliance with good laboratory practice, the evaluation of multiple dose levels, and the duration of exposure that involved most of the lifespan.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

4.1.1 *Humans*

2-Mercaptobenzothiazole has been detected in the urine samples of four workers employed at a plant producing 2-mercaptobenzothiazole, one worker from the administration department of the plant, and one out of forty persons not knowingly exposed to 2-mercaptobenzothiazole. Most 2-mercaptobenzothiazole in the urine was excreted in conjugated forms (e.g. 2-mercaptobenzothiazole glucuronide) rather than in its unchanged form (Gries et al., 2015).

4.1.2 Experimental systems

(a) Absorption, distribution, and excretion

An early study of pharmacokinetics after subcutaneous administration of radiolabelled 2-mercaptobenzothiazole to guinea-pigs demonstrated that the compound was well absorbed, with abrasion increasing the rate of absorption. Distribution occurred primarily in the kidney, liver, and thyroid gland. The thyroid gland contained the highest concentration of the compound 48 hours after injection. Ninety percent of the compound was conjugated with glucuronides and sulfates (cited in NTP, 1988).

When administered by gavage, the half-life of 2-mercaptobenzothiazole in Fischer 344 rats was less than 8 hours, possibly as short as 4–6 hours. Absorption was rapid and was not affected by doses up to 55 mg/kg bw. The major products of metabolism were polar metabolites, consistent with the findings of earlier studies in rats and guinea-pigs (cited in NTP, 1988).

After administration in Fischer 344 rats treated by gavage, 2-mercaptobenzothiazole-derived radioactivity in the blood decreased very little between 24 and 96 hours, suggesting that residual 2-mercaptobenzothiazole-derived material accumulated in the blood. After intravenous administration in Fischer 344 rats, whole blood, plasma, urine, and faeces were analysed for radioactivity at multiple time-points, from 5 minutes up to 72 hours. Most of the radiolabel (91–96%) was excreted in the urine and 4–15% in the faeces by 72 hours. A small amount (1.5–2%) remained in the erythrocytes. The metabolites found in the urine samples were the same as those found after gavage (el Dareer et al., 1989).

(b) Metabolism

In rats treated by intraperitoneal injection, the urinary metabolites of [^{35}S-mercapto]-2-mercaptobenzothiazole comprised glutathione and glucuronic acid conjugates, and inorganic sulfate (Colucci & Buyske, 1965).

4.2 Mechanisms of carcinogenesis

The evidence on the key characteristics of carcinogens (Smith et al., 2016), concerning whether 2-mercaptobenzothiazole modulates receptor-mediated effects and is genotoxic, is summarized below. Studies relevant to whether 2-mercaptobenzothiazole induces chronic inflammation are presented in Section 4.5.

4.2.1 Receptor-mediated effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

The ability of leachates from rubber tyre materials to stimulate aryl hydrocarbon receptor (AhR)–DNA binding and AhR-dependent gene expression was recently demonstrated using recombinant mouse hepatoma (Hepa1c1c7)-based clonal cell lines containing a stably integrated AhR/dioxin-responsive element and a luciferase reporter gene with different intracellular locations and stabilities. Among the individual components of the leachates that might be involved in receptor-mediated effects, 2-mercaptobenzothiazole was identified as an AhR agonist (He et al., 2011).

2-Mercaptobenzothiazole has also been shown to inhibit rat and porcine thyroid peroxidase activity in vitro (Paul et al., 2013) and to interfere with the thyroid hormone pathway in a standard in-vivo protocol in larvae of the amphibian *Xenopus laevis* (Tietge et al., 2013). These findings were corroborated in a subsequent study that measured the inhibition of thyroid peroxidase derived from pig thyroid glands, and the inhibition of thyroxine release in a *X. laevis* thyroid gland explant culture assay and in a 7-day in-vivo assay in *X. laevis* (Hornung et al., 2015).

2-Mercaptobenzothiazole appears to accumulate in the rat thyroid after gavage (el Dareer et al., 1989; see Section 4.1.2).

4.2.2 Genetic and related effects

See Table 4.1 and Table 4.2

(a) Humans

No data in exposed humans were available to the Working Group.

In one study in vitro, 2-mercaptobenzothiazole did not induce micronucleus formation in human gastric and lung carcinoma cell lines (MGC-803 and A549, respectively) (Ye et al., 2014).

(b) Experimental systems

Zinc mercaptobenzothiazole, the zinc salt of 2-mercaptobenzothiazole, did not induce chromosomal aberrations in the bone marrow of Swiss albino mice 36 hours after administration of a single intraperitoneal dose of the compound. Groups of four mice received three different doses (480, 960, and 1920 µg/20 g) [24, 48 and 96 mg/kg bw] (Mohanan et al., 2000).

In male and female Fischer 344 rats, 2-mercaptobenzothiazole (375 mg/kg bw by gavage) did not bind to DNA in any of the tissues examined (liver, adrenal glands, pituitary gland, pancreas, and bone marrow) (Brewster et al., 1989).

2-Mercaptobenzothiazole induced chromosomal aberrations and sister-chromatid exchange in Chinese hamster ovary (CHO) cells in the presence of a metabolic activation system, as well as mutations at the $Tk^{+/-}$ locus in mouse L5178Y lymphoma cells (NTP, 1988). It also induced polyploidy in Chinese hamster lung (CHL) cells in the presence and absence of a metabolic activation system (Matsuoka *et a*l., 2005). However, it gave negative results for the induction of 6-thioguanine-resistant mutants (*Hgprt* gene mutation) in Chinese hamster V79 cells (Donner et al., 1983).

2-Mercaptobenzothiazole was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, in the presence or absence of metabolic activation (NTP, 1988). A previous study also reported negative results in *S. typhimurium*, although the purity of the compound and the dose were not specified (Donner et al., 1983). Similarly, 2-mercaptobenzothiazole was reported to give negative results in an early study in *Escherichia coli* SD-4-73, but the purity and doses tested were not indicated (Szybalski, 1958). More recently, 2-mercaptobenzothiazole also gave negative results when tested in *S. typhimurium* TA1535/psK1002 (Ye et al., 2014).

4.3 Data relevant to comparisons across agents and end-points

For all compounds evaluated in the present volume of the *IARC Monographs*, including 2-mercaptobenzothiazole, analyses of high-throughput screening data generated by the Tox21 and ToxCast™ research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013) are presented in the *Monograph* on 1-bromopropane, in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

The major effect of 2-mercaptobenzothiazole identified in humans is allergic contact dermatitis, which has been reported in numerous case studies after contact with synthetic rubber gloves (Cao et al., 2010; Tomc et al., 2012), rubber ear plugs (Deguchi & Tagami, 1996), or condom catheters (Harmon et al., 1995), after working in the production of photographic films (Rudzki et al., 1981), or in a mining industry in which xanthate, carbamate and 2-mercaptobenzothiazole were used (Sasseville et al., 2003), after being issued

Table 4.1 Genetic and related effects of 2-mercaptobenzothiazole in human and other mammalian systems

Species, strain, sex	Test system	End-point	Test	Results		Dose (LED or HID)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Human	Gastric MGC-803 and lung A549 cell lines	Chromosomal damage	Micronuclei	–	–	100 µg/mL (not cytotoxic)		Ye et al. (2014)
Mouse, Swiss albino, NR	Bone marrow	Chromosomal damage	Chromosomal aberrations	–	NA	96 mg/kg bw i.p.; single dose (zinc salt of MBT)		Mohanan et al. (2000)
Rat, Fischer 344, M/F	Liver, adrenal and pituitary glands, pancreas, bone marrow	DNA damage	DNA binding	–	NA	375 mg/kg bw by gavage		Brewster et al. (1989)
Mouse	L5178 lymphoma cells	Mutation	*Tk*$^{+/-}$	–	+	100 µg/mL without and 5 µg/mL with metabolic activation		NTP (1988)
Chinese hamster	Lung (V79)	Mutation	*Hgprt*	–	NT	300 µg/mL		Donner et al. (1983)
Chinese hamster	Lung (CHL)	Chromosomal damage	Chromosomal aberrations	+	+	200 µg/mL without and 400 µg/mL with metabolic activation	Toxicity at 400 µg/mL without, and 600 µg/mL with, metabolic activation	Matsuoka et al. (2005)
Chinese hamster	Ovary (CHO)	Chromosomal damage	Chromosomal aberrations	–	+	30 µg/mL without and 352 µg/mL with metabolic activation		NTP (1988)
Chinese hamster	Ovary (CHO)	Chromosomal damage	Sister-chromatid exchange	–	+	20 µg/mL without and 352 µg/mL with metabolic activation		NTP (1988)

+, positive; –, negative; bw, body weight; F, female; HID, highest ineffective dose; Hgprt, hypoxanthine-guanine phosphoribosyltransferase; i.p., intraperitoneal; LED, lowest effective dose; M, male; MBT, 2-mercaptobenzothiazole; NA, not applicable; NR, not reported; NT, not tested; Tk, thymidine kinase locus

Table 4.2 Genetic and related effects of 2-mercaptobenzothiazole in non-mammalian systems

Species, strain	End-point	Test	Results		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Salmonella typhimurium, strain NR	Mutation	Reverse mutation	(–)	(–)	NR	Purity and dose NR; response stated to be statistically non-significant	Donner et al. (1983)
Salmonella typhimurium, TA100, TA1535, TA1537	Mutation	Reverse mutation	–	–	0–1000 µg/plate		NTP (1988)
Salmonella typhimurium, TA98	Mutation	Reverse mutation	–	±	0–1000 µg/plate		NTP (1988)
Salmonella typhimurium, TA98, TA100, TA1535, TA1537	Mutation	Reverse mutation	–	–	0–10 000 µg/plate		NTP (1988)
Salmonella typhimurium, TA1535/psK1002	DNA damage	SOS/*umu* test	–	–	19 µg/mL without or 20 µg/mL with metabolic activation	50% lethal concentration: 19 µg/mL without metabolic activation and 20 µg/ml with metabolic activation	Ye et al. (2014)
Escherichia coli, SD-4-73	Mutation	Reverse mutation	(–)	NT	NR	Purity and dose NR	Szybalski (1958)

+, positive; –, negative; (–), negative in a study of limited quality; ±, equivocal (variable response in several experiments within an adequate study); HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested with hand-based splints made of neoprene that is known to contain 2-mercaptobenzothiazole and its derivatives and formaldehyde (Stern et al., 1998), or after contact with an oil containing 2-mercaptobenzothiazole when making moulds (Wilkinson et al., 1990). The number of actual cases of allergic contact dermatitis attributed to mercapto mix and 2-mercaptobenzothiazole reported to EPIDERM in the United Kingdom from 1996 to 2012 was 177 (Warburton et al., 2015). An analysis of 803 female cleaners who were evaluated for contact dermatitis and 64 736 female controls without occupational dermatitis showed that the cleaners were significantly more frequently sensitized to 2-mercaptobenzothiazole (Liskowsky et al., 2011). In a positive patch-test analysis of 75 patients (38 men and 37 women) with contact allergic dermatitis, 6.66% (4 men and 1 woman) of the subjects tested showed reactivity to 2-mercaptobenzothiazole (Singhal & Reddy, 2000). Among 25 patients who showed a positive reaction to xanthates or other rubber additives, four patients showed reactivity to carbamate mix, thiuram mix, and 2-mercaptobenzothiazole, suggesting cross-reactivity of these chemicals (Sasseville et al., 2007). In 43 young people (31 men and 12 women) with eczematous skin lesions, two of the most frequent substances that showed a positive result in a patch test were thiurams (23.3%) and 2-mercaptobenazothiazole (20.9%) (Ventura et al., 2001).

In-vitro studies showed dose-dependent increases in cell-associated interleukin-18 in human skin cells (Corsini et al., 2009, 2013). In the human monocytic cell line THP-1, increased surface markers of CD54 and CD86 (An et al., 2009) and secretion of macrophage inflammatory protein-1β was detected (Hirota & Moro, 2006).

4.5.2 Experimental systems

The major effects of 2-mercaptobenzothiazole other than carcinogenicity identified in a 2-year bioassay in rats were nephropathy characterized by tubular hyperplasia in exposed males, and ulcers and inflammation of the forestomach in exposed males and females (NTP, 1988). Cell proliferation in the draining lymph nodes was increased by exposure of mice to sensitizers, including 2-mercaptobenzothiazole (Ikarashi et al., 1993; Ahuja et al., 2009).

One study showed that haptenation occurs through the formation of mixed disulfides between the thiol group on 2-mercaptobenzothiazole and a protein sulfhydryl group (Chipinda et al., 2007). 2-Mercaptobenzothiazole can conjugate with lysine or cysteine (Wang & Tabor, 1988b). [The Working Group noted the possibility that the thiol group of 2-mercaptobenzothiazole may react either via oxidation and/or thioester formation with carboxylate groups of amino acids.]

5. Summary of Data Reported

5.1 Exposure data

2-Mercaptobenzothiazole is a chemical of high production volume that is mainly used as an accelerator in the manufacture of rubber products and as an inhibitor of corrosion. Workers are exposed during the production of 2-mercaptobenzothiazole, and can be exposed during the manufacture of tyres and rubber products and the production of pesticides. The general population is exposed to 2-mercaptobenzothiazole through dermal contact with consumer goods containing rubber. 2-Mercaptobenzothiazole has also been detected in samples of urban air, presumably originating from tyre abrasion, and in samples of effluent water from rubber manufacturers and tanneries.

5.2 Human carcinogenicity data

Studies on the carcinogenicity of 2-mercaptobenzothiazole were available for a plant that manufactured chemicals for the rubber industry in north Wales, United Kingdom, and for a general chemical manufacturing plant in West Virginia, USA.

The study on the plant in Wales was described in a series of reports. The Working Group considered that this study was the more informative of those available. Comparisons of exposed workers with the national population of England and Wales showed a significant excess of incident cases of cancer of the urinary bladder. Internal comparisons that controlled for other occupational exposures showed a non-significant trend in increasing incidence of cancer of the urinary bladder with increasing cumulative exposure to 2-mercaptobenzothiazole. A non-significant twofold excess risk was observed in the group with highest exposure.

The study in the plant in the USA reported a statistically significant fourfold excess of mortality from cancer of the urinary bladder based on a small number of deaths in a subgroup of workers exposed to 2-mercaptobenzothiazole, but with no documented exposure to 4-aminobiphenyl (classified in IARC Group 1 as a cause of cancer of the urinary bladder). A statistically significant trend in mortality from cancer of the urinary bladder with increasing cumulative exposure to 2-mercaptobenzothiazole was also observed.

The lack of available data on tobacco smoking was a limitation of both studies; however, confounding by smoking is unlikely to explain the exposure–response patterns observed in these studies.

5.3 Animal carcinogenicity data

2-Mercaptobenzothiazole was tested for carcinogenicity by oral administration in two studies in male and female mice (one of these studies was considered to be inadequate for an evaluation) and in one study in male and female rats.

In one study in male and female mice, oral administration (by gavage) of 2-mercaptobenzothiazole induced a significantly increased incidence of hepatocellular adenoma or carcinoma (combined) in female mice; in male mice, 2-mercaptobenzothiazole did not result in any significant increase in tumour incidence.

In the study in male and female rats, oral administration (by gavage) of 2-mercaptobenzothiazole to male rats induced a significantly increased incidence of benign pheochromocytoma and of pheochromocytoma (benign or malignant, combined) of the adrenal gland, with a significant positive trend, and was also associated with a significantly increased incidence of mononuclear cell leukaemia of the haematopoietic system, pancreatic acinar cell adenoma, preputial gland adenoma, preputial gland adenoma or carcinoma (combined), pituitary gland adenoma and tumours of the skin (fibroma, neurofibroma, sarcoma or fibrosarcoma, combined). A significant positive trend in the incidence of mesothelioma (multiple organs) was also observed. In female rats, oral administration (by gavage) of 2-mercaptobenzothiazole resulted in a significantly increased incidence of benign pheochromocytoma of the adrenal gland and of adenoma of the pituitary gland, with a significant positive trend.

5.4 Mechanistic and other relevant data

A study of workers reported urinary excretion of 2-mercaptobenzothiazole glucuronide. In rodents, the compound is well absorbed, and distribution primarily to the kidney, liver, and thyroid gland occurs after subcutaneous administration. Urinary excretion accounts for > 90% after intravenous administration to rats. In rats, the major urinary metabolites are glutathione and glucuronic acid conjugates.

With respect to the key characteristics of human carcinogens, there is *moderate* evidence that 2-mercaptobenzothiazole modulates receptor-mediated effects. 2-Mercaptobenzothiazole acted as an agonist of the aryl hydrocarbon receptor in an assay in mouse hepatoma cells. 2-Mercaptobenzothiazole also inhibited rat and pig thyroid peroxidase in vitro, and inhibited thyroxine release from *Xenopus laevis* thyroid gland ex vivo and in vivo. ToxCast data supported activation of the aryl hydrocarbon receptor pathway by 2-mercaptobenzothiazole in human cells and in assays for development in zebrafish.

There is *weak* evidence that 2-mercaptobenzothiazole is genotoxic. 2-Mercaptobenzothiazole induced chromosomal aberrations and sister-chromatid exchange in Chinese hamster ovary cells in the presence of a metabolic activation system, and caused mutations at the *Tk* locus in mouse L5178Y lymphoma cells. However, it was not mutagenic in test systems in bacteria or in human gastric and lung carcinoma cell lines, and did not bind to rat DNA in vivo.

The evidence that 2-mercaptobenzothiazole induces chronic inflammation is *weak*. 2-Mercaptobenzothiazole is a contact allergen in humans. It increased the levels of interleukin-18 in human skin cells, and caused inflammation of the forestomach in male and female rats in a 2-year bioassay.

There were few data on the other key characteristics of human carcinogens (is electrophilic or can be metabolically activated, alters DNA repair or causes genomic instability, induces epigenetic alterations, induces oxidative stress, is immunosuppressive, causes immortalization, or alters cell proliferation, cell death, or nutrient supply).

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of 2-mercaptobenzothiazole. A positive association has been observed between exposure to 2-mercaptobenzothiazole and cancer of the urinary bladder.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-mercaptobenzothiazole.

6.3 Overall evaluation

2-Mercaptobenzothiazole is *probably carcinogenic to humans (Group 2A)*.

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